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THE EMBRYOLOGICAL SIGNIFICANCE OF CERTAIN LESIONS OF THE PREPUCE AND NEIGHBOURHOOD.

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THE object of the following paper is to draw attention to some of the lesions occasionally met with in the region of the prepuce and anterior part of the urethra, and their relationship to the embryology of the parts.

The histological investigations involved were carried out in the Embryology Laboratory of the University of Glasgow, and my thanks are due to Dr. James F. Gemmill for much friendly help and advice.

Some years ago[1] I published several examples of cysts in the region of the raphé of the prepuce and of the penis. I propose now to give some notes of further cases which have come under my observation.

In the first of the papers referred to above, attention was directed to the relationship of these cysts to the development of the penis and urethra. Since then, however, anatomists have thrown further light on the development of the urethra and prepuce. I touched upon this in a paper[2] on malformations of the penis, contributed in 1907 to the Section of Diseases of Children at the Exeter meeting of the British Medical Association, but I wish again to refer to it before proceeding to describe the cases.

I.—EMBRYOLOGY.

Urethra.—On the under (caudal) surface of the genital papilla the cloacal plate forms a mesial ridge, extending forwards to the apex of the papilla, where it forms an epithelial horn, produced by a thickening of the surface ectoderm. The urogenital opening results from a breaking through of the cloacal plate behind and at the base of the genital papilla. By a loosening of the central cells of the mesial ridge, derived from the cloacal plate in front of the urogenital opening, a groove is produced (Fig. 1, p. 2), running on to the caudal face of the genital papilla.[3] This is the *urethral groove.* The groove is closed from behind forwards to form the spongy portion of the urethra, and the line of junction of the lips of the groove (inner genital folds) is indicated externally by an epidermal ridge—the raphé.

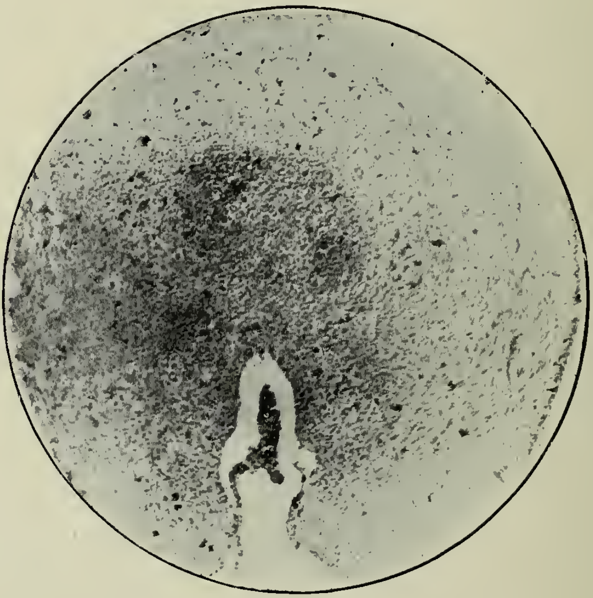

Fig. 1.

Transverse section of genital eminence at about third month. Epithelium not well preserved, but shows hollowing to form urethral groove. (Microphotograph by Dr. Leonard Findlay.)

The mesoderm of the lips of the groove, passing across the line of junction, completely separates, in the normal course of development, the urethra from the epidermis, except anteriorly at the meatus. This brings us to the consideration of the development of the prepuce and the terminal portion of the urethra.

Prepuce and terminal (glandular) portion of the urethra.—The development of the prepuce must be considered from two standpoints—(1) its external conformation, and (2) its separation internally from the glans. As regards (1), the presence on its under surface of a raphé, continuous with that of the penis and terminating in the frænum, points to the prepuce being *originally open below*, and so forming there the anterior extremity of the urethral groove. Its closure is brought about by the coalescence of the inner genital folds which form the lips of the groove. That there must subsequently be a growth forwards of this part of the prepuce is shown by the fact that at birth the raphé is present on the most anterior part of the prepuce, which is well beyond the tip of the glans, and it runs back thence on the inner surface of the prepuce to terminate at the frænum. (2) The differentiation of the prepuce from the glans is, according to Mr. Wood Jones,[4] brought about by an ingrowth, at the distal end of the genital papilla or tubercle, of epithelium from the skin covering the tubercle. This ingrowth "sculptures out the glans from the overlying skin. The cell invasion also burrows into the glans itself, and forms the urethra (at first as a solid plug) within the glans." The

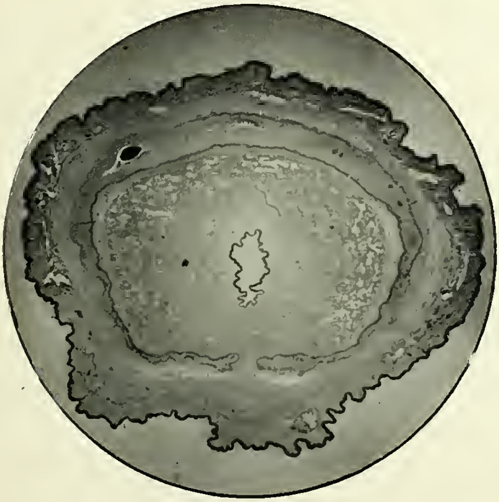

Fig. 2.

Transverse section of penis at seventh month, through anterior part of glans, showing epithelial ingrowth between skin and glans. To left, on dorsum, is cavity containing deeply-stained granular material. (× 12.)

central cells of the urethral plug break down and form the terminal portion of the urethra, a process which is completed by the seventh month. The epithelial ingrowth between the glans and the skin covering it splits into two laminæ by the breaking down of its central cells. A space lined by epithelium is thus formed between the skin and the glans. The outer lamina forms the epithelium of the mucous layer of the prepuce, and the inner the epithelium of the glans, continuous at the meatus with the urethral lining. The separation into two laminæ is scarcely begun by the seventh month, and frequently is not complete at the time of birth. I have been able to confirm these last statements by sections of the distal portion of the penis of a seven months' fœtus, and by clinical experience.

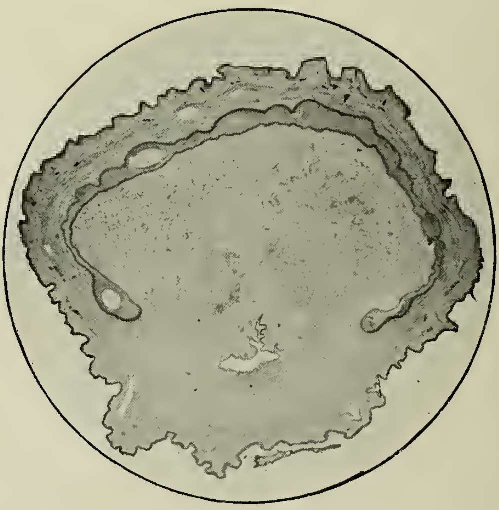

FIG. 3.

Section through posterior part of glans. Areas of cleavage more numerous than in Fig. 2. (× 12.)

Coronal sections through the anterior part of the glans at the seventh month show that the glans is, except at the region of the frænum, completely separated from the superficial fascia by a band of stratified epithelium (Fig. 2, p. 3). The periphery of this epithelial band is formed by a single layer of columnar cells with deeply-stained nuclei. As the centre of the band is approached the cells become larger, of rounded or polygonal outline, and with more faintly-stained nuclei, while in some places they form "nests" surrounded by flattened epithelium. In other parts of the band the cells in the centre become somewhat flattened and do not stain well, and here and there we find cavities or clefts containing desquamated flat cells. The largest of these cavities contains, in addition, a mass of deeply-stained coarse granular material.

Sections through the posterior part of the glans, cutting through the anterior extremities of the corpora cavernosa, show that the epithelial band does not extend so far round on the under surface: its horns, in conformity with the oblique course of the corona, stop short at a level dorsal to that of the urethra (Fig. 3, p. 4). The areas of cleavage are more frequent than in sections farther forward, and flattening of the cells of the central layers is much more marked. The cavities contain concentrically arranged squames, and have well-defined walls, whose structure closely approximates that of the epidermis (Fig. 4). In the greater frequency of these cavities, and the better definition of their

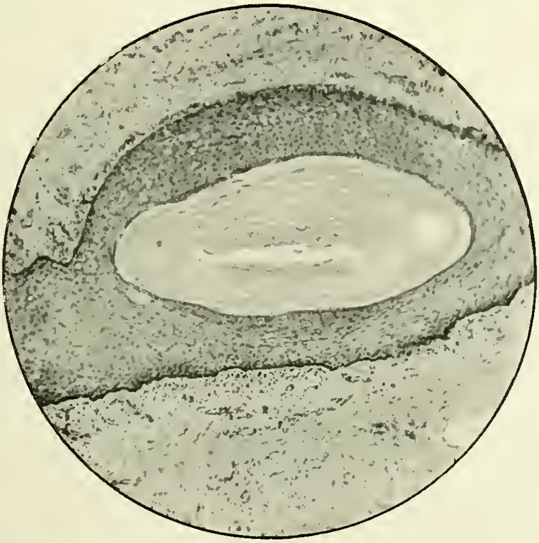

FIG. 4.

Cavity in epithelial ingrowth, to left of dorsum in Fig. 3. Cavity contains desquamated cells, and shows formation of cell-nest at one side. Epithelium bounding cavity very regular. (× 66.)

walls, I think we have evidence that the splitting up of the epithelial ingrowth takes place from behind forwards, and I shall show below how this is borne out by clinical experience. The characters of the different layers of cells in the epithelial ingrowth agree with the description given by Dr. Berry Hart.[5] With regard to the formation of the glandular urethra, I am not at present in a position to speak, but the appearances in mild degrees of hypospadias (*vide infra*) point to its having an origin distinct from the spongy urethra.

II.—DEFECTS AND ERRORS IN DEVELOPMENT.

Urethra.—(*a*) *Defective development of the epithelial plug* which invades the glans may occur and complete atresia result (Wood Jones[6]). It is more common, however, to meet with a moderate degree of stenosis of the meatus, the lower part of the orifice being occluded by a membranous septum.

(*b*) *Deficiency in the closure of the urethral groove* results in the condition of hypospadias. The deficiency is most frequently found at the anterior end of the penile urethra—glandular hypospadias. This coincides with the point of junction of the glandular urethra with the urethral groove—the part of the groove which is the last to close.

As I have elsewhere shown,[2] the prepuce is, in a large proportion of these cases, externally quite well formed (52·6 per cent); but there is also a large number (42 per cent) in which there is a deficiency in its ventral portion, in which cases the prepuce is said to be "hooded." If the prepuce is completely formed externally, the urethral defect is often not recognised until circumcision has been performed. In cases of glandular hypospadias, it is usual to find a dimple or a gutter on the glans. Such a depression points to a defect in the formation of the glandular urethra. Imperfect or defective closure of the lips of the penile urethral groove is rarely associated with a completely formed glandular urethra. I am able to give particulars of but one such case in my own practice (*vide infra*, Case I).

A rare result of defective closure of the groove is the formation of a urethral diverticulum.[7]

(*c*) *Error in closure* may take the form of external abnormality, and is exemplified in the various forms of malformation or deviation of the raphé. These are comparatively common, and I have already[2] detailed a considerable number of cases.

A second abnormality, very rare, arises from an epithelial "rest" in the line of closure. I was fortunate in meeting an example of this several years ago.[8] In this case the "rest" had developed into a tubular cyst on the under surface of the penis.

Prepuce.—(*a*) *Defective development:* The complete development of the prepuce, if by this is meant not only its external conformation but also the separation of its mucous layer from the epithelium of the glans, does not. as a rule, take place till some time after birth. If an attempt be made to retract the prepuce before this separation is complete it is found that "adhesions" require to be broken down. In the most extreme degree of this defect the movable prepuce is absent, and the skin of the penis is continued forward over the glans and joins the urethral epithelium at the meatus. Such cases have been reported by Loyano.[9] Mr. Wood Jones[10] figures a specimen of absence of both prepuce and glandular urethra.

As regards external conformation, we have the "hooded" prepuce which accompanies the higher degrees of hypospadias, and which is also found in a considerable percentage of cases of glandular hypospadias. In the prepuce which presents this malformation there is not only the ventral deficiency, but also, as a rule, more marked differentiation than usual of the lateral and dorsal portions of the prepuce from the glans.

(*b*) *Errors of development.*—The remarks on errors in the closure of the urethra (*q.v.*) are applicable to the prepuce. The raphé may deviate from its normal form and course, or cyst-formation may take place, or the two conditions may coexist. It has to be remembered, however, that in this region there is a second potential origin for cysts, viz., the epithelial ingrowth which is concerned with the origin of the preputial fold. I have not seen any examples of cyst with this origin, but cysts of Tyson's glands[11] have been described.

III.—Clinical.

Adhesions between prepuce and glans.—A certain degree of union of the prepuce with the glans may be looked upon as the rule at birth and for some time afterwards; it is the exception to meet with cases where in young infants the prepuce is freely retractable. The degree of union varies. In some cases, when the prepuce is pulled back, the glans and mucous surface of the prepuce are found to be thinly coated with a material resembling lard; in others the union is so complete in parts that when it is broken down bleeding occurs. There is usually no union in the immediate vicinity of the meatus; and in circumcising infants and young children it is not an uncommon experience to find that, when the mucous layer is stripped back from the glans, the surface of the latter is, with the exception of the circum-meatal area and the sulcus behind the corona, quite raw. This raw surface often requires dressing for several weeks before it assumes the appearance of normal epithelium. In some cases, indeed, it cicatrises, and remains for a considerable time at a lower level than that of the circum-meatal area. In the sulcus behind the corona separation has usually taken place by the

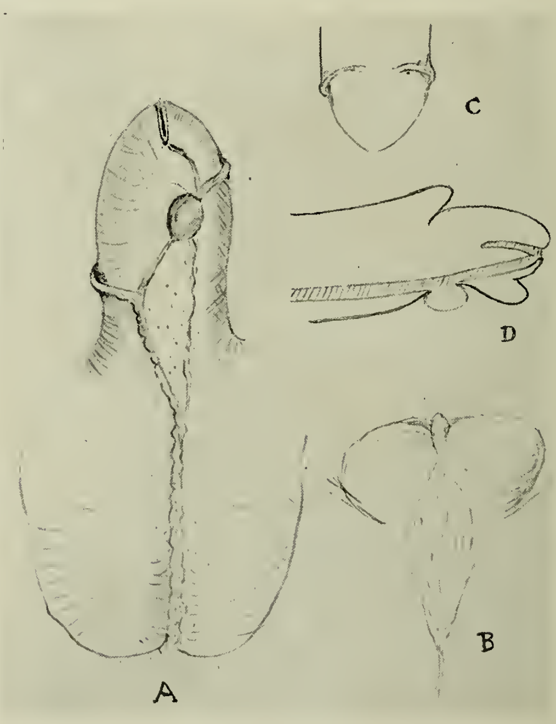

Fig. 5 (Case 1).

A, appearance of parts from below. B, conformation of perineal raphé. C, termination of branches of raphé on dorsum of prepuce. D, diagrammatic representation of urethra, with lacuna magna and pseudocyst. (From sketches at time of operation.)

accumulation of smegma, and this bears out the opinion already expressed when considering the microscopical appearances (*vide supra*), that the splitting up of the epithelial ingrowth takes place from behind forward.

Atypical closure of urethral groove.—The first of the following cases represents a condition where the urethral groove had closed normally, except at or near its anterior end, where, just behind the prepuce, there had been a deficient growth of mesoderm. The result was that the floor of the urethra was in contact with the epidermis, and ballooned out with urine during the act of micturition. The glandular portion of the urethra had been completely formed, but the meatus was smaller than normal. The particulars are as follows:—

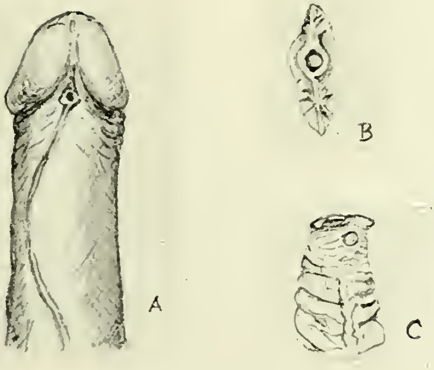

Fig. 6.

A, general appearance of under surface of penis in Case II, showing devious raphé and crateriform pit near frænum (from sketch at time of operation). B, appearance of depression after hardening (natural size). C, appearance of parts in Case III after hardening (natural size).

Case I.—*Abortive hypospadias, bent penis, and malformed raphé: glandular urethra complete; at seat of deficiency, pseudocyst, which afterwards ruptured.*—J. W., aged 2 years, was brought to the dispensary of the Royal Hospital for Sick Children in December, 1909, on account of difficulty in micturition. Examination showed phimosis and ventral curving of the penis. An anæsthetic was administered, and while this was being done he micturated. On turning up the bent penis a prominent clear cyst-like structure was found in the middle line, a little behind the preputial orifice. The "cyst," which collapsed on being handled, lay under one limb of a much malformed raphé, and was *firmly anchored to the deeper parts,* so that when the skin of the penis was pushed forwards it overlapped the cystic swelling. The raphé of the perineum was widespread, enclosing a lenticular area of irregular skin. On the anterior surface of the scrotum it was double, and ultimately bifurcated. The right limb of the bifurcation was very prominent, and passed on to the right side of the penis to beyond the root, and again sub-divided into right and left. The right branch passed forwards and outwards and terminated on the dorsum of the prepuce; the left passed forwards and inwards to the middle line and terminated in the "cyst." The left limb of the original bifurcation was faintly marked, and ran forwards in a straight line to the "cyst," whence it was continued forward to the preputial orifice after giving off a branch to the left. This last branch ran on to the dorsum of the prepuce, where it terminated opposite to the branch from the right limb at a spot distal to the level of the corona glandis (Fig. 5, p. 8).

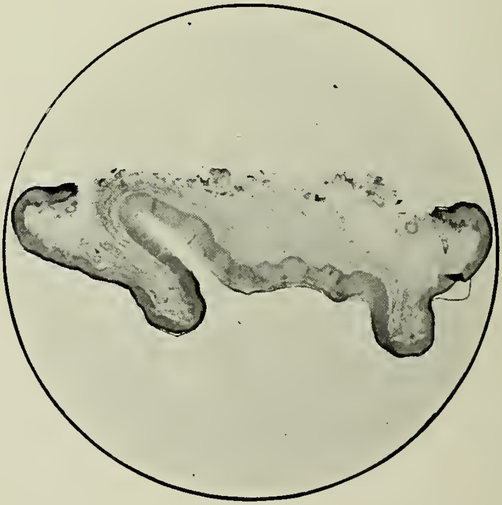

FIG. 7 (Case II).

Transverse section showing depression lined with epidermis, and extending on left well under margin of opening. (× 12.)

On dilating and retracting the prepuce a tiny meatus was found on the under surface and near the tip of the glans. A probe could be passed along the urethra for a distance of a quarter of an inch (0·6 cm.), at which point it came to a dead stop. No trace of any other orifice was visible.

The prepuce was divided longitudinally on its dorsal aspect, and the cut edges of the skin were sutured to those of the mucous layer.

Ten days later he was again anæsthetised for the purpose of more thoroughly examining the relationship of the parts. There was some obstruction of the meatus by dried discharge. During his struggles while going under the anæsthetic he passed urine through a fine orifice in front of the centre of the "cyst," and then urine came also through the meatus, the two jets of urine being expelled simultaneously. A probe passed into the meatus came to a stop as before; another, introduced into the opening in the "cyst" and passed forwards, emerged at the ventral part of the meatus. It was then found that a probe passed into the meatus and well towards the floor easily entered the urethra, and could be seen shining through the translucent wall of the cyst. If the probe were passed straight

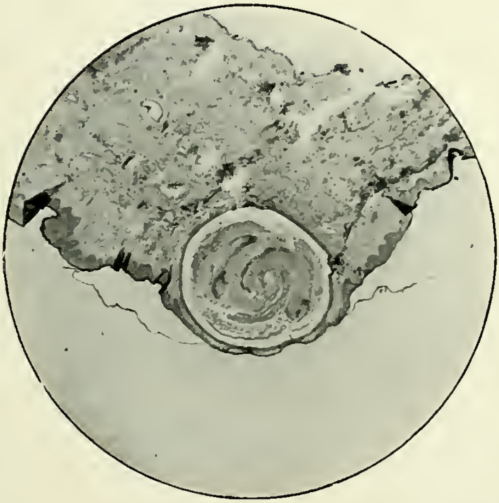

Fig. 8 (Case III).

Shows epidermal cyst containing desquamated epithelium, and umbilication of epidermal surface of prepuce slightly to right in figure. (× 12.)

into the meatus it evidently entered a lacuna. The arrangement of the parts is diagrammatically shown in the figure. The chief points of interest in this case are the malformation of the raphé, the complete development of the glandular urethra, and the pseudocyst.

The remaining three cases are examples of cysts of the ventral surface of the prepuce.

Case II. *Incomplete cystic formation, resembling ulcer.**—W. S., aged 22, 4th April, 1902, had noticed, about five years before, a small "blister" on the under surface of the penis, a little way behind the frænum. The blister had ruptured, and had since continued to discharge.

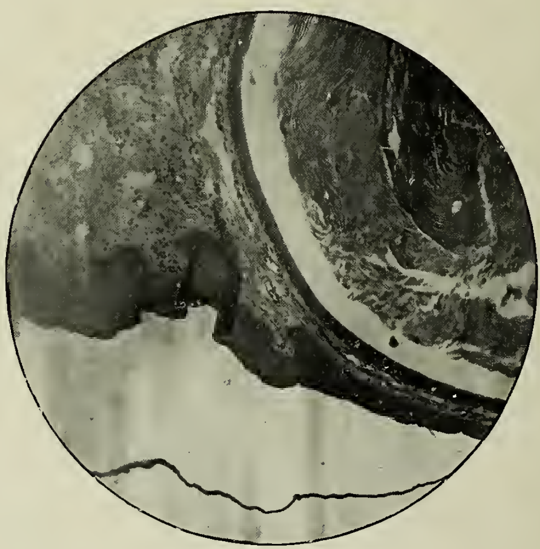

Fig. 9.

Same as last, but more highly magnified to show details of epithelial lining of cyst. (× 66.)

Situated on the raphé, about half an inch (1·25 cm.) posterior to the frænum, was a small elevation with sloping sides, which terminated in a central crater. The condition resembled, and was looked on as, a slightly depressed ulcer. No discharge could be squeezed from the crater, and there was nothing suggesting a cyst. The raphé was otherwise well-formed, but deviated to the right about the middle of the penis, coming back to the middle line again as it approached the frænum (Fig. 6, p. 9).

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* Same as Case XLI in series in *British Medical Journal*, September, 1907.

After injection of the region with cocaine, an elliptical piece of skin containing the "ulcer" was snipped away with curved scissors, and the edges of the wound were closed with catgut suture. Fig. 6, B (p. 9), represents the appearance of the specimen (actual size) after hardening in spirit.

Occupying the raphé is a depression, 0·2 cm. in diameter, surrounded by a raised margin. Sections cut transversely to the long axis of the raphé show that the supposed ulcer is really a recess lined by skin, and overhung by one margin of the external opening (Fig. 7, p. 10). The lining consists of stratified epithelium, which differs from that of the prepuce in the following particulars:—(1) It is more bulky; (2) the deepest (basal) cells are not so regularly arranged; (3) interpapillary processes occur on only one side of the recess, and are ill-formed; (4) absence of the stratum granulosum; and (5) the protoplasm of the superficial layers in the deeper part of the recess is unstained, so that the nuclei lie in the meshes of a deeply-stained network.

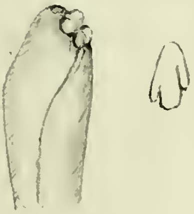

FIG. 10 (Case IV).

From sketch at time of operation (natural size). Shows bilocular appearance of cyst. Small figure on right, reconstruction of plan of cyst, from below (magnified).

CASE III. *Cyst in median line.*—L. H., aged $2\frac{2}{12}$, 14th September, 1903, the subject of slight phimosis and of hydrocele, presented also a cyst on the under surface of the prepuce immediately in the line of the raphé. The cyst was opaque, yellow, not much larger than the head of an ordinary pin, and resembled one of the multiple sebaceous cysts which are not infrequently seen on the scrotum and penis.[12]

In the hardened specimen (Fig. 6, C, p. 9), the raphé is not recognisable further forward than a point 3 mm. behind a small cyst-like structure, which has a diameter of slightly over 1·5 mm. Sections cut transversely to the long axis of the raphé show a cyst whose wall is composed of fibrous tissue lined by stratified, considerably flattened epithelial cells (Figs. 8 and 9, pp. 11, 12). In the most superficial part of the cyst the epithelium comes into direct contact and apparently blends with epidermis. As the point where this blending takes place is approached, the cells of the most external layers of the cyst-wall are observed to have become much bulkier, approximating in appearance the deeper layers of epidermis, and at the spot where the cyst-wall is blended with the epidermis the bulky cells of the former form a continuous layer, which separates the flatter cells of the cyst-wall from the equally flat epidermal layers. It is noticed,

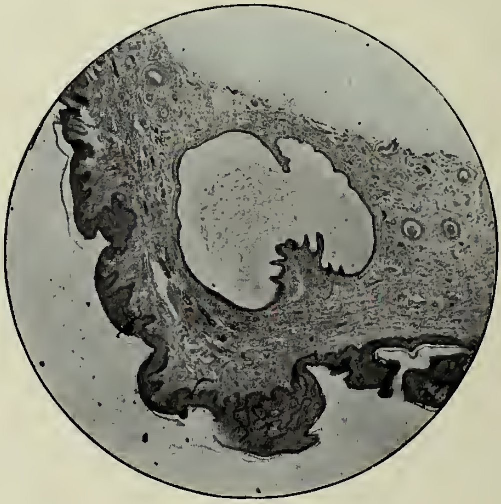

Fig. 11.

Shows outline of cyst in Case IV, on transverse section, a little in front of junction of loculus on left with main cyst. Section shows extremities of crescentic edge of septum as downgrowth from above and upgrowth from below. (× 12.)

further, that at this point the epidermal surface of the prepuce is slightly umbilicated.

CASE IV. *Mucous cyst.*—M. M., aged $1\frac{5}{12}$, 1st February, 1909, was seen on account of phimosis. There was some deviation of the raphé. On pulling the foreskin back as far as possible a cyst was seen under the raphé, which here was situated well to the left of the middle line. The cyst was translucent and was situated near the anterior end of the external layer of the prepuce. It appeared at first to be double, but was not really so, pressure causing the contents of one swelling to pass into the other (see Fig. 10, p. 13, from a sketch made at the time). After removing the prepuce by circumcision the cyst was punctured, and some clear mucous fluid escaped. No exact measurements of the cyst were taken; but it was of elongated shape and lay under and in line of the raphé. It seemed to consist of more than one chamber, as it did not collapse after being punctured. An interrupted series of sections was cut from before backwards

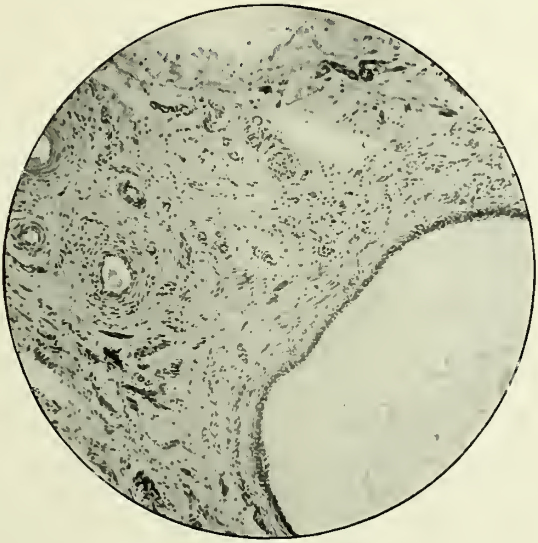

FIG. 12 (Case IV).

Higher magnification to show character of epithelial lining of cyst. (× 66.)

transversely to the long axis of the raphé. From this series it was possible to reconstruct the outline of the cyst. The cyst-cavity is single in front; but as we pass backwards it is seen to become divided into two by a septum, which passes obliquely from the right ventral to the left dorsal part of the cyst-wall. The anterior free edge of the septum is crescentic, and concave forwards, as is shown by its upper and lower extremities appearing in sections earlier in the series than those which contain the complete septum (Fig. 11, p. 14). As we continue to pass backwards the septum is shifted more and more to the left, the left loculus becomes smaller and finally disappears, and we have again a single cavity. Still further back another septum separates a small loculus on the right. We thus have a main cyst joined on the left side by a loculus which opens forward, and further back a smaller loculus joins the main cavity on the right (see Fig. 10, p. 13). The microscopical structure of the cyst-wall differs from that found in Cases II and III. There is nowhere any continuity with the epidermis. The fibrous outer wall is composed of

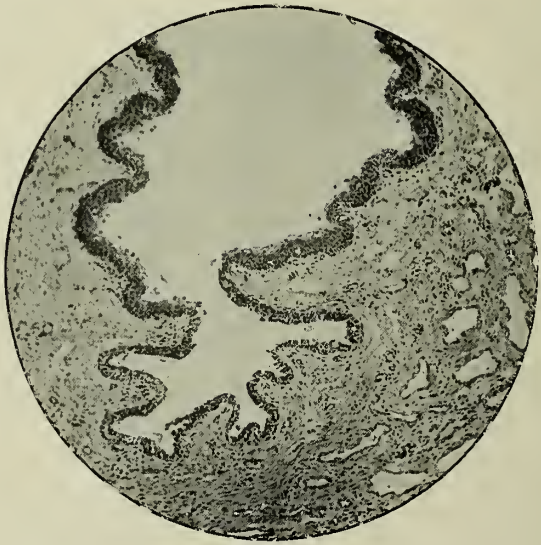

Fig. 13.

Ventral portion of glandular urethra at seventh month, to contrast with preceding figure. (× 66.)

closely set connective tissue, with elongated nuclei which here and there suggest those of muscle-cells. This is lined by epithelium, as a rule in two layers, but increased in some parts to four or five. The inner cells are long and cubical or globular, and the clear body of the cell projects well beyond the nucleus (Fig. 12, p. 15). External to the connective tissue of the wall is the lower subcutaneous tissue, containing many blood-vessels. The cavity of the cyst contains fine granular material resembling precipitated mucus.

The epithelium lining the cyst is comparable to that of the urethra in the seven-months' fœtus (Fig. 13, p. 16); but in the latter the inner layer is distinctly columnar, and there are numerous shed cells in the urethral lumen.

Remarks.

In Case I, we have an example of defective growth of the mesoderm: and the fixation of the cyst-like structure on the deeper parts was the feature which first led to a true appreciation of its nature.

The remaining cases (II, III, and IV) form a series in which the different results of error (formation of epithelial "rests") in the closure of the urethral groove are exemplified. Case II may be looked on as the simplest form. In it we have an example of a skin-lined recess, the opening of which may have been at one time completely closed by epithelium, or have been temporarily occluded by a plug of desquamated cells from the interior of its cavity. Whatever the primary condition, distension of the cavity had occurred, and was followed by rupture and discharge of the contents. In Case III the cyst was completely closed, and, both in its epithelial lining and the nature of its contents, presented characters similar to those of an "implantation" cyst. It is possible that the difference (flattening) between its epithelium and that of Case II depended on the fact that in the latter all tension was absent, and had been so for a considerable time. Case IV differs from both of the preceding in the shape of its cavity, and in the character of its epithelium and contents. Its epithelium tends towards the urethral rather than to the epidermal type, and despite its superficial situation when first noticed it has probably arisen from the deeper cells of the inner genital folds, *i.e.*, cells which would ultimately assume the characters of urethral epithelium. It approximates the specimen described by Thöle,[13] in which a moniliform cyst showed on section flattened cells on its floor and columnar on its roof.

One particular is common to all three cases—their situation in the region of the raphé. In Case III, I have no note regarding the condition of the raphé; but in Cases II and IV it ran a devious course.

When the situation and structure of these cysts are taken into consideration along with the embryology of the parts, I think we are justified in assuming their congenital origin—in other words, their dependence on faulty closure of the urethral groove.

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